REMARKS

Claims 1-8, 24-35, 38 and 40-55 are presently pending. Claims 28-33 and 40-46 have been withdrawn from consideration as being drawn to a non-elected invention.[1] New claim 55 has been added. Support for new claim 55 is found in the present specification at least at page 23, lines 2-3. No new matter has been added.

Applicants gratefully acknowledge the Examiner's indication that claims 1, 2, 4-8, 25, 34, 35, 38, 51 and 53 are allowable over the art of record.

Applicants reserve their right to prosecute the subject matter of any canceled claim, any amended claim, any withdrawn claim or any other unclaimed subject matter in one or more divisional, continuation or continuation-in-part applications.

I. The Rejection Under 35 U.S.C. § 102(b)

Claim 24 has been rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by U.S. Patent No. 4,202,827 to Tzikas *et al.* ("Tzikas"). In particular, the Examiner has alleged that Example 12 of Tzikas anticipates claim 24 of the present application. Applicants respectfully traverse this rejection.

Claim 24 of the present application is directed to a pharmaceutical composition comprising an anthrapyrazole compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or a pharmaceutically acceptable diluent. Example 12 of Tzikas describes the synthesis and isolation of crude anthrapyrazole material, but does not describe anything which one skilled in the art would consider to be a pharmaceutical composition.[2] In other words, the slurry of anthrapyrazole in water resulting from the process of Example 12, which may or may not still contain sulfuric acid, is not an acceptable formulation for human administration and, thus, is not a pharmaceutical composition.

The Examiner has pointed to page 23, lines 2-3 of the present specification for the proposition that the water used in Example 12 of Tzikas is an acceptable liquid carrier. Applicants respectfully point out that page 23, lines 2-3 of the present specification recite

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[1] Applicants have not yet elected to cancel the unelected subject matter in anticipation of possible rejoinder.

[2] Applicants submit that the composition of Example 12 of Tzikas would not meet the Food and Drug Administration's current good manufacturing practice (cGMP) regulations. In other words, it would not be suitable for human use, particularly for parenteral use which requires stringent sterilization.

"sterile water" as a pharmaceutically acceptable carrier. Tzikas does not disclose sterile water or any other pharmaceutically acceptable carrier or diluent which would be acceptable for human administration, that is Tzikas does not disclose a pharmaceutical composition. Indeed, Tzikas teaches that the anthrapyrazole compounds are useful as vat dyes, the synthesis and isolation of which would not require pharmaceutical grade solvents. *See* Tzikas at column 1, lines 64-65. Thus, Applicants respectfully submit that the procedure set forth in Example 12 of Tzikas does not produce a pharmaceutical composition as claimed in either claim 24 or new 55.

Accordingly, in view of the above remarks, Applicants respectfully submit that the rejection of claim 24 under 35 U.S.C. § 102(b) cannot stand and must be withdrawn.

II. The Rejection Under 35 U.S.C. § 103(a)

Claims 3, 26, 27, 52 and 54 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 4,556,654 to Showalter *et al.* ("Showalter"). Applicants respectfully traverse this rejection.

As Applicants argued in the previous response, the fact that a claimed subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994). There still must be some suggestion or motivation, either in the cited reference or generally known to one of ordinary skill in the art, to modify the reference to arrive at the claimed compounds. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). In other words, the Examiner must point to some source of motivation for one of ordinary skill in the art to pick and choose the particular variables from the generic class of Showalter to arrive at the claimed invention. Applicants submit that no such source has been provided which would motivate one of ordinary skill in the art to select a subgenus of Showalter wherein the variable Z is required to be H and the variable X and Y are required to be the substituents set forth in claims 3, 26 and 27 (wherein claims 52 and 54 are pharmaceutical composition claims depending from claims 3 and 26, respectively). Applicants submit that Showalter does not provide the requisite motivation to arrive at the claimed subgeneric classes and, as discussed below, actually teaches away from the claimed invention when considered as a whole.

The Examiner has stated that the consideration of a reference is not limited to the preferred or working embodiments, but extends to the entire disclosure. *Application of Boe*, 355 F.2d 961, 965 (1966). Applicants agree, but respectfully submit that in considering a

reference in its entirety, portions that lead away from the claimed invention must also be considered. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983); MPEP 2141.02.

In fact, portions of a reference that teach away from the claimed invention are particularly relevant when evaluating the obviousness of a subgenus encompassed by a prior art genus. The United States Patent and Trademark Office guidelines for considering the obviousness of a subgenus in view of a prior art genus, as derived from Federal Circuit law, require that any teaching or suggestion in a reference of a preferred subgenus that is significantly different in structure from the claimed subgenus be considered in determining obviousness. MPEP 2144.08; *In re Baird*, 16 F.3d at 382-3. Indeed, the Federal Circuit held that disclosure indicating a preference leading away from the claimed compounds may weigh heavily against a determination of obviousness. *In re Baird*, 16 F.3d at 383. Thus, Applicants agree that the prior art reference must be considered as a whole, including portions that teach away from the claimed invention, and, as discussed below, respectfully submit that the structure-activity relationship data as a whole set forth in Showalter would discourage one of ordinary skill in the art from selecting a subgenus wherein Z is H, or at the very least, does not provide the requisite motivation to select such a subgenus.

The Examiner points to listed compound 6 in the table at columns 25-28, which is unsubstituted at N-2, and states that the compound has better activity than some compounds which are substituted at N-2. Applicants agree with this statement. Listed compound 6 shows better antibacterial activity against certain organisms and weaker antibacterial activity against other organisms relative to the other compounds in the table. Applicants do not suggest that this data teaches away from the presently claimed compounds[3]; however, Applicants strongly submit that this table does not provide any motivation to one of ordinary skill in the art to select a subgenus of compounds wherein N-2 is unsubstituted.

Applicants do submit, however, that contrary to the Examiner's assertion, the *in vitro* data against human colon adenocarcinoma cells in columns 37 and 38 of Showalter does teach away from the presently claimed compounds. The Examiner has stated that this data shows that some N-2 substituted compounds (*i.e.*, listed compounds 3, 16, 29 and 32) have the same or less activity than the N-2 unsubstituted compound (*i.e.*, listed compound 4).

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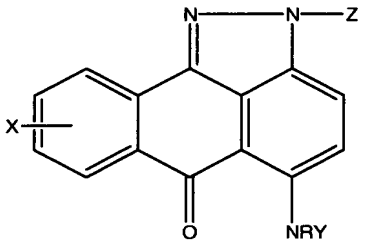
[3] Applicants do note that the fact that only 1 compound out of a total of 79 total compounds tested for antibacterial activity was unsubstituted at N-2 (*i.e.*, listed compound 6) suggests that compounds unsubstituted at N-2 were not of particular interest.

Again, Applicants agree that certain N-2 substituted compounds have less activity than the N-2 unsubstituted compound and do not intend to suggest that N-2 unsubstituted compounds are inactive. However, Applicants respectfully submit that the Examiner has incorrectly compared the N-2 unsubstituted compound (*i.e.*, listed compound 4) to N-2 substituted compounds which have additional differences at sites other than N-2. Specifically, listed compounds 3 and 16 have different NRY groups than listed compound 4, listed compound 29 has a different X group than listed compound 4, and listed compound 32 has different X and NRY groups than compound 4. Thus, differences in activity between listed compound 4 and listed compounds 3, 16, 29 and 32 are not solely attributable to the substitution at N-2.

Applicants submit that the relevant comparison is between listed compound 4 and compounds which only differ by having a substituent at the N-2 position. This is the comparison one of ordinary skill in the art would make to determine the affect of the N-2 substituent on activity, as it is the only difference in structure. As set forth below, listed compounds 5 and 18 are identical to listed compound 4 with the exception of the Z group (*i.e.*, the substituent at the N-2 position). Showalter does not provide data for any other compounds identical to listed compound 4 with the exception of the substitution at N-2 (other than the antibacterial data previously discussed).



Listed Compound	X	Z	NRY	ID_{50} Molar
4	H	H.HCl	$NH(CH_2)_2NH(CH_2)_2OH$	1.5×10^{-6}
5	H	CH_3.HCl	$NH(CH_2)_2NH(CH_2)_2OH$	4.0×10^{-7}
18	H	$(CH_2)_2NH_2$.2HCl	$NH(CH_2)_2NH(CH_2)_2OH$	6.8×10^{-8}

Data taken from columns 37-38 of Showalter.

This comparison demonstrates that when all other substituents are held constant, adding a methyl group at N-2 increases the anti-tumor activity by over an order of magnitude and further modifying the compound to include an alkylamino group at N-2 increases the anti-tumor activity by another order of magnitude. Thus, this data would lead one of ordinary skill in the art away from selecting a subgenus wherein N-2 is unsubstituted.

In summary, Applicants submit that Showalter does not provide the requisite suggestion or motivation to arrive at the claimed invention. Furthermore, when the antibacterial data and anti-tumor data of Showalter are considered as a whole, Applicants submit that the results teach away from the selection of a subgenus of Showalter wherein Z is H.

Accordingly, in view of the above remarks, Applicants respectfully submit that the rejection of claims 3, 26, 27, 52 and 54 under 35 U.S.C. § 103(a) cannot stand and must be withdrawn.

III. Objection to claims 47-50

Claims 47-50 are objected to as being dependent upon a rejected base claim. Applicants respectfully submit that all presently pending claims are in condition for allowance in view of the above amendments and remarks and that the objection to claims 47-50 must be withdrawn.

IV. Conclusion

Applicants respectfully submit that all of the pending claims are now in condition for allowance. If the Examiner still disagrees, she is invited to call the undersigned to schedule an interview to resolve any remaining concerns.

It is believed that no fee is due in connection with this Reply; however, in the event any fee is required, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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